The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Stephen Hurdle

Dated 6 October 2003

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
A
16 SEP 2002
RECEIVED BY FAX

The Patent Office

1/77

16SEP02 E748583-1 D02944
P01/7700 0.00-0221438.5

Request for grant of a patent

See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — SMC 60542/GB/P1

2. Patent application number *(The Patent Office will fill in this part)* — 16 SEP 2002 — 0221438.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Avecia Limited
Hexagon House
Blackley
Manchester, M9 8ZS
United Kingdom

Patents ADP number *(if you know it)* 07764137001

If the applicant is a corporate body, give the country/state of its incorporation — GB

4. Title of the invention — PROCESSES AND COMPOUNDS

5. Name of your agent *(if you have one)* — REVELL, Christopher

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Avecia Limited
Hexagon House
Blackley
Manchester, M9 8ZS
United Kingdom

Patents ADP number *(if you know it)* 6969885001 06969885004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Patents Form 1/77

16-SEP-2002 15:12 FROM:HOECHST PLC

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	13
Claim(s)	05 DML
Abstract	02
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Date

Avecia Limited Authorised Signatory

12. Name and daytime telephone number of person to contact in the United Kingdom — Mrs K.M. Pinder/Miss G. Terry 0161 721 1361/2

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*

e) *Once you have filled in the form you must remember to sign and date it.*

f) *For details of the fee and ways to pay please contact the Patent Office.*

SMC 60542

APPLICANTS

AVECIA Ltd

TITLE

PROCESSES AND COMPOUNDS

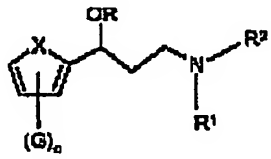
PROCESSES AND COMPOUNDS

This invention relates to processes for the preparation of heterocyclic hydroxyamines and to novel substituted heterocycles.

Heterocyclic hydroxyamines are important intermediates in the synthesis of many pharmaceuticals . For example Duloxetine ((+)-N-methyl-3-(1-naphthalenyloxy)-2-thiophenepropanamine), a 5-HT and norepinephrine uptake inhibitor, is showing considerable promise as a potential treatment for depression and urinary incontinenance (US 5,023,269, US 4,956,388 and for a review see Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2000), 1(1), 116-121).

Processes for the manufacture of Duloxetine have been described in Deeter, et al., Tetrahedron Letters, 31(49), 7101-04 (1990); EP654264; US5,023,269; Liu et al., Chirality, 12(1), 26-29 (2000); EP457559;and Wheeler et al., J. Labelled Compd. Radiopharm, 36(3), 213-223 (1995).

According to the present invention there is provided a process for the preparation of a compound of Formula (1)



Formula (1)

wherein:

X is S, O or NR^3, wherein R^3 is H or an organic group;

R is H or an organic group;

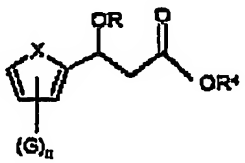
R^1 and R^2 each independently are H, optionally substituted alkyl or optionally substituted aryl;

G is a substituent; and

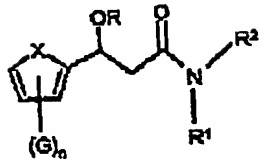
n is 0 to 3;

which comprises the steps:

(a) reacting a compound of Formula (2) with a compound of Formula NHR^1R^2 to give a compound of Formula (3)



Formula (2)



Formula (3)

wherein X, R, G and n are as defined above and R^4 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl or a combination thereof; and

(b) reducing the compound of Formula (3) to give a compound of Formula (1).

A second aspect of the invention provides a process for the preparation of a compound of Formula (3) whereby a compound of Formula (2) is reacted with a compound of Formula NHR^1R^2 to give a compound of Formula (3).

A third aspect of the invention provides a process for the preparation of a compound of Formula (1) in which a compound of Formula (3) is reduced to give a compound of Formula (1).

When X is NR^3, then R^3 is preferably H, optionally substituted alkyl or optionally substituted aryl, more preferably H or optionally substituted C_{1-4}alkyl. It is especially preferred that when X is NR^3 then R^3 is H.

Preferably X is S.

Preferably n is 0.

Preferably R is H, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heterocyclyl or a combination thereof or a hydroxy protecting group such as benzyl, benzoyl or tetrahydropyranyl.

When R is optionally substituted alkyl, optionally substituted alkene or optionally substituted alkyne it may be a linear, branched or cyclic molecule.

It is particularly preferred that R is H; optionally substituted alkyl, especially optionally substituted C_{1-4}alkyl; or optionally substituted aryl, especially optionally substituted phenyl or optionally substituted napthyl.

It is especially preferred that R is H or napthyl.

Optional substituents for R are preferably selected from: alkyl (preferably C_{1-4}-alkyl), optionally substituted alkoxy (preferably C_{1-4}-alkoxy), optionally substituted aryl (preferably phenyl), optionally substituted aryloxy (preferably phenoxy), polyalkylene oxide (preferably polyethylene oxide or polypropylene oxide), carboxy, phosphato, sulpho, nitro,

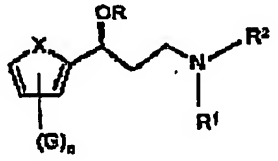
cyano, halo, ureido, $-SO_2F$, hydroxy, ester, $-NR^aR^b$, $-COR^a$, $-CONR^aR^b$, $-NHCOR^a$, carboxyester, sulphono, and $-SO_2NR^aR^b$ wherein R^a and R^b are each independently H or optionally substituted alkyl (especially C_{1-4}-alkyl) or, in the case of $-NR^aR^b$, $-CONR^aR^b$ and $-SO_2NR^aR^b$, R^a and R^b together with the nitrogen atom to which they are attached represent an aliphatic or aromatic ring system; or a combination thereof.

The substituent G is preferably selected from the optional substituents as for R.

Preferably R^1 and R^2 are H or optionally substituted C_{1-4}alkyl. In a preferred embodiment one of R^1 and R^2 is H and the other is optionally substituted C_{1-4}alkyl. In an especially preferred embodiment one of R^1 and R^2 is H and the other is methyl.

Optional substituents for R^1 and R^2 are preferably selected from: optionally substituted alkoxy (preferably C_{1-4}-alkoxy), optionally substituted aryl (preferably phenyl), optionally substituted aryloxy (preferably phenoxy), polyalkylene oxide (preferably polyethylene oxide or polypropylene oxide), carboxy, phosphato, sulpho, nitro, cyano, halo, ureido, $-SO_2F$, hydroxy, ester, $-NR^aR^b$, $-COR^a$, $-CONR^aR^b$, $-NHCOR^a$, carboxyester, sulphone, and $-SO_2NR^aR^b$ wherein R^a and R^b are each independently H or optionally substituted alkyl (especially C_{1-4}-alkyl) or, in the case of $-NR^aR^b$, $-CONR^aR^b$ and $-SO_2NR^aR^b$, R^a and R^b together with the nitrogen atom to which they are attached represent an aliphatic or aromatic ring system; or a combination thereof.

Preferably compounds of Formula (1) prepared by a process according to the invention are of Formula (4).



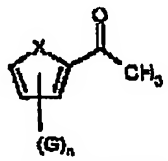
Formula (4)

wherein X, G, n, R, R^1 and R^2 are as defined above.

In a compound of Formula (2) R^4 preferably is optionally substituted alkyl or optionally substituted aryl, more preferably optionally substituted C_{1-12} alkyl or optionally substituted benzyl. It is especially preferred that R^4 is optionally substituted C_{1-4} alkyl, particularly ethyl.

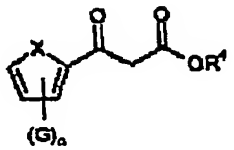
Preferred optional substituents for R^4 are as for R^1 and R^2.

Compounds of Formula (2) are preferably formed by acylating a compound of Formula (5)



Formula (5)

where X, G and n are as defined above, to give a compound of



Formula (6)

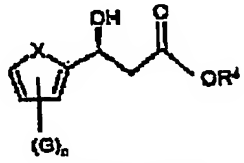
where X, G, n, and R^4 are as defined above, followed by reduction of the *Beta*-keto group so formed and optionally alkylating the hydroxyl group so formed.

The compound of Formula (5) is preferably acylated by a dialkyl carbonate.

Reduction of the *Beta*-keto group in compounds of Formula (6) may be carried out by any means known in the art to be able to reduce *Beta*-keto groups in compounds such as those of Formula (6).

Preferably the reduction of the *Beta*-keto group in compounds of Formula (6) is achieved by reaction with a hydrogen source other than hydrogen gas. The hydrogen source is preferably formic acid; iso-propanol; cyclohexadiene; an organic formate salt, especially triethylamine or ammonia; an inorganic formate salt, especially potassium, sodium or lithium. More preferrably reduction of the *Beta*-keto group in compounds of Formula (6) to give a compound of Formula (2) may be by reaction with a mixture a of formic acid and triethylamine, preferably in a molar ratio of formic acid to triethylamine of from 10:1 to 1:2 and especially in a molar ratio of 5:2.

The reduction of the *Beta*-keto group in compounds of Formula (6) is preferably a stereospecific reduction. The product of this reduction may be either the (S) or the (R) isomer. Preferably the product is produced in at least 80% e.e., more preferably in at least 90% e.e., and especially in at least 95% e.e. Preferably the product of the reduction is a compound of Formula (7).



Formula (7)

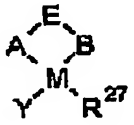
Where X, G, n and R^4 are as defined above.

When reduction of the *Beta*-keto group in a compound of Formula (6) is a stereospecific reduction it may be carried out by any means known in the art for the stereospecific reduction of *Beta*-keto groups. These include the use of chemical catalysts (for examples see Genet, J. P.; Ratovelomanana-Vidal, V.; Cano de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* 1995, 36, 4801; Guerreiro, P.; Cano de Andrade, M. C.; Henry, J. C.; Tranchier, J. P.; Phansavath, P.; Ratvelomanana-

Vidal, V.; Genet, J. P.; Homri, T.; Touati, A. R.; Ben Hassine, B. *C.R. Acad. Sci. Paris* 1999, 2, 175; which are incorporated herein by reference; also reactions as described in "Catalytic Asymmetric Synthesis" by Ojima, published by Wiley-VGH (ISBN 0-471-40027-0) and "Principle and Applications of Asymmetric Synthesis by Lin, Li and Chan published by Wiley inter-science (ISBN 0-471-29805-0)) or a biological catalyst such as a whole cell, an enzyme, a cell preparation or a cell free extract.

Preferred catalysts are those asymmetric transfer hydrogenation catalysts which are described in WO97/20789, WO98/42643, and WO02/44111 which are herein incorporated by reference.

Preferred transfer hydrogenation catalysts for use in the process of the present invention have the general formula:



wherein:

R^{27} represents a neutral optionally substituted hydrocarbyl, a neutral optionally substituted perhalogenated hydrocarbyl, or an optionally substituted cyclopentadienyl ligand;

A represents an optionally substituted nitrogen;

B represents an optionally substituted nitrogen, oxygen, sulphur or phosphorous;

E represents a linking group;

M represents a metal capable of catalysing transfer hydrogenation; and

Y represents an anionic group, a basic ligand or a vacant site;

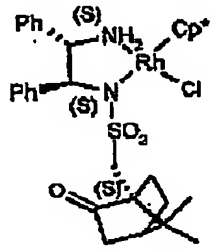
provided that at least one of A or B comprises a substituted nitrogen and the substitutent has at least one chiral centre; and

provided that when Y is not a vacant site that at least one of A or B carries a hydrogen atom.

Particularly preferred transfer hydrogenation catalysts are those Ru, Rh or Ir catalysts of the type described in WO97/20789, WO98/42643, and WO02/44111 which comprise an optionally substituted diamine ligand, for example optionally substituted ethylene diamine ligands, and a ligand which is selected from the group comprising optionally substituted neutral aromatic ligands, for example p-cymene, and optionally substituted cyclopentadiene ligands.

Especially preferred are Ru, Rh or Ir catalysts of the type described in WO97/20789, WO98/42643, and WO02/44111 which comprise an optionally substituted diamine ligand wherein at least one nitrogen atom of the optionally substituted diamine ligand is substituted with a group containing a chiral centre, particularly a suphonyl group containing a chiral centre.

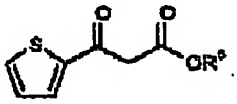
One example of these especially preferred catalysts can be prepared by reacting rhodium pentamethylcyclopentadiene dichloride dimer with (S)-N-camphorsulphonyl-(S,S)-diphenylethylenediamine under the conditions described in Example 6 of WO98/42643 to give a catalyst of Formula



Cp* = Pentamethylcyclopentadiene

This reaction may optionally be carried out under biphasic conditions and is preferably carried out in the absence of oxygen, for example under a nitrogen atmosphere. The preferred temperature range for this reaction is -30 to 90 °C, especially 0 to 50°C.

When X is S, preferred compounds of Formula (2), including compounds of Formula (8),



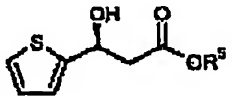
Formula (8)

where R^5 is optionally substituted C_{1-6}alkyl.

may be prepared by reacting 2-acetyl thiophene with a dialkyl carbonate, more preferably diethyl carbonate, in the presence of a base preferably an alkali salt of the alkyl salt corresponding to the dialkylcarbonate (eg sodium ethoxide if the dialkyl carbonate is diethyl carbonate), a non-nucleophilic base such as NaOtBu, KOtBu, LiOtBu, lithium diisopropylamide, Na, K or Li hexamethyldisylazide, Na in liquid ammonia, sodamide or an amine base with an activating Lewis acid (eg triethylamine with a Mg salt). Especially preferred bases are hydride salts, particularly sodium hydride and non-nucleophilic bases, particularly NaOtBu.

R^5 is preferably optionally substituted C_{1-4}alkyl and especially ethyl.

The compound of Formula (8) is then preferably reduced by a stereospecific reduction, as described above, to give a compound of Formula (9):



Formula (9)

where R^5 is as described above.

The amidation of the compound of Formula (2) in step (a) may be carried out by any means known in the art.

Preferably Step (a) of the process is performed in the presence of any organic solvent or mixture of organic solvents which is unreactive towards the reagents employed. Polar aprotic solvents are especially favoured. Examples of suitable solvents include toluene , tetrahydrofuran, acetonitrile, DMF and ethers.

Step (a) of the invention is preferably carried out in the temperature range of from –20°C to 150°C. More preferably in the temperature range of from -10°C to 100°C.

Step (a) of the process is advantageously allowed to proceed to at least 90% and more advantageously at least 95% conversion to a compound of Formula (3).

The reaction time of step (a) of the process of the second aspect of the invention will depend on a number of factors, for example the reagent concentrations, the relative amounts of reagents, the presence of a catalyst, the nature of the solvent and particularly the reaction temperature. Typical reaction times, in addition to the reagent addition times, range from 1 minute to 200h hours, with reaction times of 5 minutes to 6 hours being common.

When, in a preferred embodiment of the invention, one of R^1 and R^2 is H and the other is methyl, then step (a) preferably comprises reacting a compound of Formula (2) with methylamine.

It is particularly preferred that the compound of Formula (2) and methylamine are both in solution in either a single or multiphase system.

A preferred solvent system for step (a) comprises water and a water immiscible solvent, especially toluene.

The reduction of the compound of Formula (3) in step (b) may be carried out using any suitable method known in the art. These methods include reduction by: lithium aluminium hydride, di-*iso*-butylaluminium hydride, lithium borohydride , lithium borohydride with methanol, catecholborane or borane or sodium borohydride preferably with an activating agent such as ethanol, CH_3SO_2H, H_2SO_4, pyridine, methanol, $TiCl_4$ or $CoCl_2$.

Preferably reduction of the compound of Formula (3) in step (b) is by lithium aluminium hydride

Step (b) of the process can be performed without any solvent but is preferably performed in the presence of any organic solvent or mixture of organic solvents which is unreactive towards the reagents employed. Examples of suitable solvents include toluene; methanol, hexane, tetrahydrofuran, ethylacetate, octanol, acetonitrile and dimethylformamide. Tetrahydrofuran is especially favoured.

Step (b) of the process is preferably performed in the absence of oxygen. Oxygen may be excluded by, for example, passing an inert gas, especially nitrogen, through the reaction mixture.

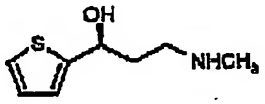
Step (b) of the process may be carried out under reduced pressure.

Step (b) of the second aspect of the invention is preferably carried out in the temperature range of from –20°C to 150°C and more preferably in the temperature range of from 10°C to 70°C.

Step (b) of the process of the second aspect of the invention is advantageously allowed to proceed to at least 90% conversion and more preferably to at least 95% conversion, to a compound of Formula (1).

The reaction time of step (b) of the process of the second aspect of the invention will depend on a number of factors, for example the reagent concentrations, the relative amounts of reagents and particularly the reaction temperature. Typical reaction times, in addition to the reagent addition times, range from 1 minute to 200 hours, with reaction times of 2 hours to 48 hours being common.

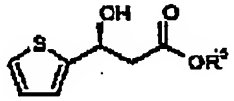
A preferred embodiment of the present invention provides a process for the preparation of a compound of Formula (10)



Formula (10)

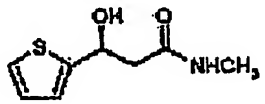
which comprises the steps:

(a) reacting a compound of Formula (9)



Formula (9)

where R^6 is optionally substituted C_{1-6}alkyl, with methylamine to give a compound of Formula (11)



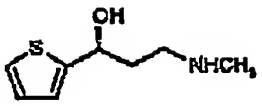
Formula (11)

and

(b) reducing the compound of Formula (11) to give the compound of Formula (10).

The preferred reductant in step (b) is lithium aluminium hydride.

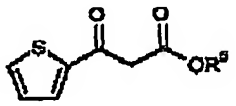
A more preferred embodiment of the present invention provides a process for the preparation of a compound of Formula (10)



Formula (10)

which comprises the steps:

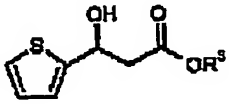
(i) acetylating 2-acetyl thiophene to give the compound of Formula (8)



Formula (8)

where R^6 is optionally substituted C_{1-8}alkyl;

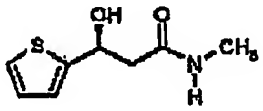
(ii) reducing the compound of Formula (8) to give the compound of Formula (9)



Formula (9)

where R^6 is optionally substituted C_{1-8}alkyl;

(iii) reacting a compound of Formula (9) with methylamine to give a compound of Formula (11);



Formula (11)

arid

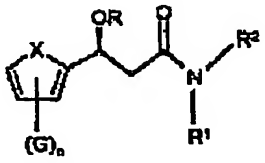
(iv) reducing the compound of Formula (11) to give the compound of Formula (10).

Conditions for steps (i) to (iv) are as described and as preferred above.

According to a fourth aspect of the invention there is provided a compound of Formula (3) as defined above.

In preferred compounds of Formula (3) R and X are as preferred in the first aspect of the invention.

A preferred compound of Formula (3) is of Formula (12).



Formula (12)

A more preferred compound of Formula (3) is of Formula (11).

Many of the compounds of Formulae (1) to (12) may exist in the form of a salt. These salts are included within the scope of the present inventions.

The compounds of Formulae (1) to (12) may be converted to the salt form using known techniques.

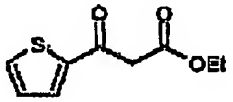
The compounds of Formulae (1) to (12) may exist in tautomeric forms other than those shown in this specification. These tautomers are also included within the scope of the present inventions.

The invention will now be illustrated, without limitation, by the following examples.

Example 1

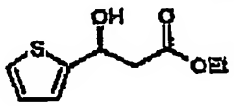
Stage 1

Preparation of ethyl-3-oxo 3-(2-thiophenyl) propanoate



Sodium hydride (60% dispersion in mineral oil, 100g, 2.5 mol) was washed with anhydrous hexane (2 x 250 ml) under a nitrogen atmosphere at room temperature. Anhydrous tetrahydrofuran (THF) (340 ml) was then added with stirring followed by 2-acetyl thiophene (136 ml, 1.25 mol) in anhydrous THF (340 ml) over period of 20 minutes. The reaction mixture was then warmed to 35°C. After 30 minutes diethyl carbonate (305.5 ml, 2.5 mol) in anhydrous THF (660 ml) was added over a period of 1 hour. After an additional hour the reaction mixture was cooled to −10°C, quenched with water (475 ml) and glacial acetic acid (145 ml) was added. The mixture was stirred for 20 minutes and then warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 200 ml). The combined organic extracts were washed with brine (2 x 200 ml), dried with Na_2SO_4 and concentrated under reduced pressure to give the title compound as a crude dark orange oil in 98% yield (242.8g).

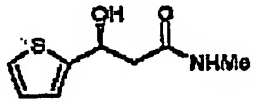
Stage 2
Preparation of ethyl-3-(S)-hydroxy 3-(2-thiophenyl) propanoate



Rhodium pentamethylcyclopentadiene dichloride dimer (1.8705 g, 0.0030 mol) and (S)-N-camphorsulphonyl-(S,S)-diphenylethylenediamine (2.582 g, 0.0061 mol) were stirred in THF (378.5 ml) at 0 °C under nitrogen to form a catalytic solution.

Ethyl-3-oxo 3-(2-thiophenyl) propanoate (300 g, 1.513 mol, from stage 1) was stirred in THF (378.5 ml) at 10 °C and sparged with nitrogen at a rate of 1.2 $Lmin^{-1}$. A portion of the catalytic solution (78.5 ml) was added, and a mixture of formic acid and triethylamine in a molar ratio of 5:2 (327.1 g) was charged at a rate of 52.1 $mlhr^{-1}$. Further portions of the catalytic solution (75 ml) were added every 1.5 hr. After the reaction had been shown to have gone to completion by GC, after about 24 hours, saturated aqueous sodium hydrogen carbonate solution (1 L) was added at room temperature to quench the reaction. The aqueous layer was extracted with toluene (400 ml). The combined organic layers were washed with brine (400 ml, 10 % w/w solution) and dried over anhydrous sodium sulphate. The organic solution was concentrated under reduced pressure to give a dark brown oil in 97.5% yield (296.4 g).

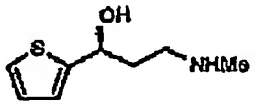
Stage 3
Preparation of 3-(S)-hydroxy-N-methyl 3-(2-thiophenyl) propanamide



Ethyl-3-(S)-hydroxy 3-(2-thiophenyl) propanoate (270 g, from stage 2) was dissolved in toluene (675 ml). To this, an aqueous methylamine solution (675 ml, 40 % w/w) was added with stirring over a period of 15 minutes at room temperature. Once the reaction had gone to completion after 1 hour, agitation was ceased and the organic layer was separated from the aqueous layer. Salt (100 g) was added to the aqueous layer which was then extracted with isopropyl acetate (2x500 ml). The organic extracts and the original organic layer were combined. Silica (250 g) was added and the resulting suspension was stirred for 20 minutes. The mixture was filtered and silica (250 g) was again added and the mixture was stirred for 20 minutes before being filtered. The resulting solution was concentrated under reduced pressure to give orange crystals (90.5 g, 36 %) as the product.

Stage 4

Preparation of (S)-3-(N-methyl) amino 1-(2-thiophenyl) propan-1-ol



3-(S)-Hydroxy-N-methyl 3-(2-thiophenyl) propanamide (80g) was dissolved in anhydrous THF (320ml) under nitrogen with stirring. A solution of lithium aluminium hydride (648ml, 1 M) in THF was added at rate that kept the temperature constant at 50 °C. When all the lithium aluminium hydride solution had been added the reaction mixture was held at 50 °C for 50 minutes. The mixture was then cooled to −10 °C and isopropanol (100 ml) was slowly added. A saturated sodium sulphate solution (310 ml) was then added and the mixture was filtered. The filter residues were washed with ethyl acetate (2x100 ml) and the aqueous layer was separated. The organic layer was washed with saturated brine (2x100 ml) and then dried over sodium sulphate. The organic solution was then concentrated under reduced pressure to give a dark orange oil (65 g, 88 %). Solvating the oil in toluene and stirring at 0 °C overnight gave crystals as the final product that were filtered and dried on the filter.

Example 2

Preparation of ethyl-3-(S)-hydroxy 3-(2-thiophenyl) propanoate by biological reduction of ethyl-3-oxo 3-(2-thiophenyl) propanoate

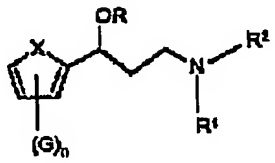
Yeast cultures were grown on YM (yeast and mold) agar at 28°C for 72h. Liquid cultures were prepared by inoculating a single colony from a plate into 50ml of sterile growth medium consisting of (per litre); glucose (10g), yeast extract (2g), trace metal solution (1ml), K_2HPO_4 (1.9g), NaH_2PO_4 $2H_2O$ (2.02g), $(NH_4)_2SO_4$ (1.8g), $MgSO_4$ $7H_2O$ (0.2g) and $FeCl_3$ (0.97mg) in a 250ml baffled flask. Following 24h growth at 28°C on an orbital shaker, the cells were harvested by centrifuging at 4000 rpm for 10 minutes and the cell pellet was resuspended in 5ml of 0.1M phosphate buffer, pH 7.5. The cell suspension was centrifuged as above, the supernatant discarded and the cell pellet resuspended in 5ml of the above buffer. Bioreductions were initiated by the addition of 5ml of cell suspension to 5ml of the above buffer containing 4g/l glucose and 20ul of ethyl-3-oxo 3-(2-thiophenyl) propanoate from Example 1 stage 1. The cells were incubated for 24h at 28°C on an orbital shaker. Formation of ethyl-3-hydroxy 3-(2-thiophenyl) propanoate was monitored by removing 1ml of cell suspension, centrifuging at 14K rpm for 1 minute to pellet the cells and analysing the supernatant by reverse phase HPLC. Analysis was performed on a Hichrom RPB column (25cm x 4.6mm i.d.) eluted at 1ml/min with 0.1% aqueous TFA and acetonitrile (70:30) at a column temperature of 28°C. The reactant and product were detected by their absorbance at 254nm. The retention time of ethyl-3-oxo 3-

(2-thiophenyl) propanoate was 12.7 minutes and the retention time of ethyl-3-hydroxy 3-(2-thiophenyl) propanoate was 9.3 minutes. Bioreduction reactions showing the formation of ethyl-3-hydroxy 3-(2-thiophenyl) propanoate were worked up by centrifuging at 4K rpm for 10 minutes and extracting the supernatant twice with an equal volume of methyl-tert-butylether. The combined extracts were dried over anhydrous sodium sulphate and then the solvent was evaporated to dryness. The residue was taken up in isohexane and 2-propanol (70:30) and the enantiomeric composition of the ethyl-3-hydroxy 3-(2-thiophenyl) propanoate was determined by chiral phase HPLC. Analysis was performed on a Chiralcel OD column (25cm x 4.6mm i.d. ex Daicel Ltd) eluted at 1ml/min with isohexane and 2-propanol (90:10) at a column temperature of 28°C. Ethyl-3-oxo 3-(2-thiophenyl) propanoate and the enantiomers of ethyl-3-hydroxy 3-(2-thiophenyl) propanoate were detected by their absorbance at 235nm. The retention time of ethyl-3-oxo 3-(2-thiophenyl) propanoate was 16.5 minutes, the retention time of ethyl-3-(S)-hydroxy 3-(2-thiophenyl) propanoate was10.3 minutes and the retention time of ethyl-3-(R)-hydroxy 3-(2-thiophenyl) propanoate was 24.0 minutes. The results are summarised in the following table.

Microorganism	% Conversion to ethyl-3-(R)-hydroxy 3-(2-thiophenyl) propanoate	% e.e. of (S) enantiomer
Saccharomyces carlsbergensis NCYC398	4	79
Hansenula wickerhamii CBS4307	51	61
Saccharomyces cerevisiae CBS431	26	80
Pichia pastoris CBS704	17	82
Debaromyces marama NCYC282	12	92
Hansenula philodendra CBS6075	10	91
Candida intermedia IFO0761	18	76
Pichia angusta NCYCR320	46	80
Candida boidinii CBS2420	66	98
Hansenula nonfermentans CBS5674	65	84
Hansenula angusta BCC426	39	93
Torulopsis sp. BCC900	26	78
Torulopsis molischiana CBS837	64	85

CLAIMS

1. A process for the preparation of a compound of Formula (1)



Formula (1)

wherein:

X is S, O or NR^3, wherein R^3 is H or an organic group;

R is H or an organic group;

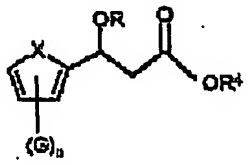
R^1 and R^2 each independently are H, optionally substituted alkyl or optionally substituted aryl;

G is a substituent; and

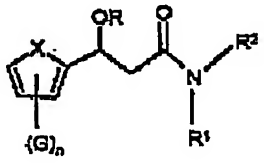
n is 0 to 3;

which comprises the steps:

(a) reacting a compound of Formula (2) with a compound of Formula NHR^1R^2 to give a compound of Formula (3)



Formula (2)

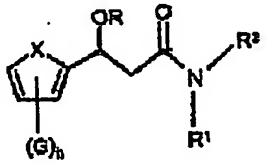


Formula (3)

wherein X, R, G and n are as defined above and R^4 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl or a combination thereof; and

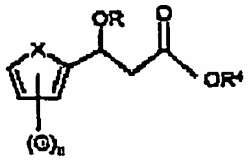
(b) reducing the compound of Formula (3) to give a compound of Formula (1).

2. A process for the preparation of a compound of Formula (3);



Formula (3)

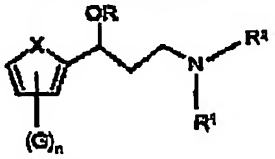
whereby a compound of Formula (2);



Formula (2)

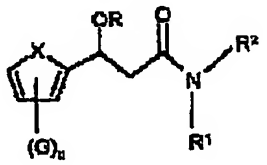
is reacted with a compound of Formula NHR^1R^2 to give a compound of Formula (3): wherein X, G, n, R, R^1, R^2 and R^4 are as defined in claim 1.

3. A process for the preparation of a compound of Formula (1);



Formula (1)

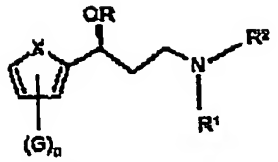
in which a compound of Formula (3);



Formula (3)

is reduced to give a compound of Formula (1): wherein X, G, n, R, R^1 and R^2 are as defined in claim 1.

4. A process according to any one of claims 1 and 3 wherein the compounds of Formula (1) are of Formula (4)



Formula (4).

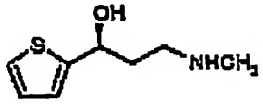
wherein X, G, n, R, R^1 and R^2 are as defined in claim 1.

5. A process according to any one of the preceding claims wherein X is S.

6. A process according to any one of the preceding claims wherein R is H or napthyl.

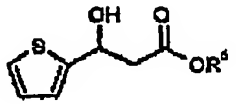
7. A process according to any one of the preceding claims wherein one of R^1 and R^2 is H and the other is methyl.

8. A process, according to any one of the preceding claims, for the preparation of a compound of Formula (10)



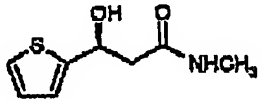
Formula (10)

which comprises the steps:
(a) reacting a compound of Formula (9)



Formula (9)

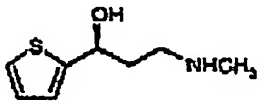
where R^5 is optionally substituted C_{1-5}alkyl, with methylamine to give a compound of Formula (11)



Formula (11)

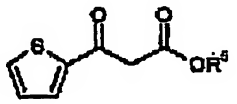
and
(b) reducing the compound of Formula (11) to give the compound of Formula (10).

9. A process, according to any one of the preceding claims, for the preparation of a compound of Formula (10)



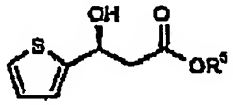
Formula (10)

which comprises the steps:
(i) acetylating 2-acetyl thiophene to give the compound of Formula (8)



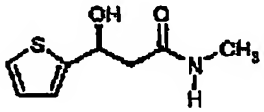
Formula (8)
where R^5 is optionally substituted C_{1-6}alkyl;

(ii) reducing the compound of Formula (8) to give the compound of Formula (9)



Formula (9)
where R^5 is optionally substituted C_{1-6}alkyl;

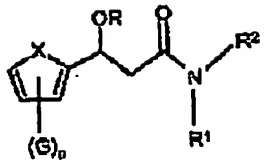
(iii) reacting a compound of Formula (9) with methylamine to give a compound of Formula (11);



Formula (11)

and
(iv) reducing the compound of Formula (11) to give the compound of Formula (10).

10. A compound of Formula (3)



Formula (3)

wherein

X is S, O or NR^3, wherein R^3 is H or an organic group;

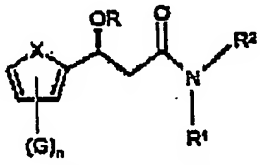
R is H or an organic group;

R^1 and R^2 each independently are H, optionally substituted alkyl or optionally substituted aryl;

G is a substituent; and

n is 0 to 3.

11. A compound of Formula (3), according to claim 10, of Formula (12);



Formula (12)

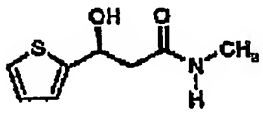
wherein X, G, n, R, R^1 and R^2 are as defined in claim 10.

12. A compound according to either claim 10 or claim 11 wherein X is S.

13. A compound according to any one of claims 10 to 12 wherein R is H or napthyl.

14. A compound according to any one of claims 10 to 13 wherein one of R^1 and R^2 is H and the other is methyl.

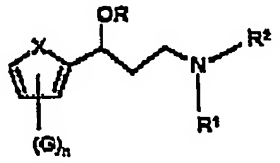
15. A compound according to any one of claims 10 to 14 of Formula (11)



Formula (11).

ABSTRACT

A process for the preparation of a compound of Formula (1)



Formula (1)

wherein:

X is S, O or NR^3, wherein R^3 is H or an organic group;

R is H or an organic group;

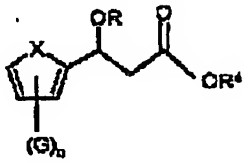
R^1 and R^2 each independently are H, optionally substituted alkyl or optionally substituted aryl;

G is a substituent; and

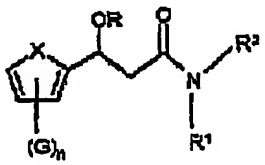
n is 0 to 3:

which comprises the steps:

(a) reacting a compound of Formula (2) with a compound of Formula NHR^1R^2 to give a compound of Formula (3)



Formula (2)



Formula (3)

wherein X, R, G and n are as defined above and R^4 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl or a combination thereof; and

(b) reducing the compound of Formula (3) to give a compound of Formula (1).

Also, a process whereby a compound of Formula (2) is reacted with a compound of Formula NHR^1R^2 to give a compound of Formula (3), a process whereby a compound of Formula (3) is reduced to give a compound of Formula (1) and novel compounds of Formula (3).